=> s tiotropium L1 5 TIOTROPIUM

=> dl1

DL1 IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system. For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> d 11

L1 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2002 ACS

RN 412010-61-8 REGISTRY

CN 3-0xa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, iodide,

(1.alpha., 2.beta., 4.beta., 5.alph

a.,7.beta.) - (9CI) (CA INDEX NAME)

OTHER NAMES:

CN tiotropium iodide

FS STEREOSEARCH

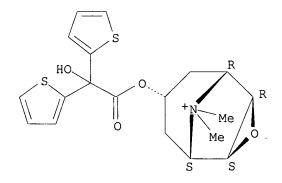
MF C19 H22 N O4 S2 . I

SR CA

LC STN Files: CA, CAPLUS, USPATFULL

CRN (186691-13-4)

Relative stereochemistry.



• 1-

6 REFERENCES IN FILE CA (1962 TO DATE) 6 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> d 2-5

L1 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2002 ACS

RN 412010-60-7 REGISTRY

CN 3-0xa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, chloride,

(1.alpha., 2.beta., 4.beta., 5.al

pha.,7.beta.)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN tiotropium chloride
FS STEREOSEARCH
MF C19 H22 N O4 S2 . C1
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (186691-13-4)

Relative stereochemistry.

● Cl -

6 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES IN FILE CAPLUS (1962 TO DATE)

ANSWER 3 OF 5 REGISTRY COPYRIGHT 2002 ACS

RN 411207-31-3 REGISTRY
CN 3-0xa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, monohydrate, (1.alpha.,2.beta.,4.beta.,5.alpha.,7.beta.)- (9CI) (CA INDEX NAME)
OTHER NAMES:

CN **Tiotropium bromide monohydrate** FS STEREOSEARCH

MF C19 H22 N O4 S2 . Br . H2 O

SR CA

L1

LC STN Files: CA, CAPLUS, USPATFULL

CRN (186691-13-4)

Relative stereochemistry.

• Br-

H₂O

8 REFERENCES IN FILE CA (1962 TO DATE) 8 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L1 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2002 ACS

RN 186691-13-4 REGISTRY

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-,

(1.alpha., 2.beta., 4.beta., 5.alpha., 7.bet a.) - (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Tiotropium

FS STEREOSEARCH

MF C19 H22 N O4 S2

CI COM

SR CA

LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, SYNTHLINE, TOXCENTER, USPATFULL

Relative stereochemistry.

35 REFERENCES IN FILE CA (1962 TO DATE)

8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

35 REFERENCES IN FILE CAPLUS (1962 TO DATE)

```
ANSWER 5 OF 5 REGISTRY COPYRIGHT 2002 ACS
L1
RN
     136310-93-5 REGISTRY
CN
     3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(hydroxydi-2-
     thienylacetyl)oxy]-9,9-dimethyl-, bromide,
(1.alpha., 2.beta., 4.beta., 5.alp
     ha.,7.beta.) - (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
     3-0xa-9-azatricyclo[3.3.1.02,4]nonane, 3-oxa-9-
     azoniatricyclo[3.3.1.02,4]nonane deriv.
OTHER NAMES:
CN
     BA 679BR
CN
     Spiriva
CN
     Tiotropium bromide
FS
     STEREOSEARCH
     C19 H22 N O4 S2 . Br
MF
     COM
CI
SR
     CA
LC
                  ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS,
     STN Files:
       CASREACT, CIN, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MEDLINE,
       MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPATFULL
         (*File contains numerically searchable property data)
CRN
     (186691-13-4)
```

Relative stereochemistry.

• Br-

54 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
54 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L3 1 BECLOMETHASONE/CN

=> d 13

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS

RN 4419-39-0 REGISTRY

CN Pregna-1,4-diene-3,20-dione, 9-chloro-11,17,21-trihydroxy-16-methyl-, (11.beta.,16.beta.)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Pregna-1,4-diene-3,20-dione, 9-chloro-11.beta.,17,21-trihydroxy-16.beta.-methyl- (7CI, 8CI)

OTHER NAMES:

CN 9-Chloro-11.beta.,17,21-trihydroxy-16.beta.-methyl-pregna-1,4-diene-3,20-dione

CN 9-Chloro-16.beta.-methylprednisolone

CN Beclometasone

CN Beclomethasone

CN Becolvent

FS STEREOSEARCH

MF C22 H29 C1 O5

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CBNB,

CEN,

CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

341 REFERENCES IN FILE CA (1962 TO DATE)

20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

341 REFERENCES IN FILE CAPLUS (1962 TO DATE)

1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> fil embase biosis medline caplus uspatfull

COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION

FULL ESTIMATED COST 23.38 23.59

FILE 'EMBASE' ENTERED AT 20:43:53 ON 14 NOV 2002 COPYRIGHT (C) 2002 Elsevier Science B.V. All rights reserved.

```
FILE 'BIOSIS' ENTERED AT 20:43:53 ON 14 NOV 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC. (R)
FILE 'MEDLINE' ENTERED AT 20:43:53 ON 14 NOV 2002
FILE 'CAPLUS' ENTERED AT 20:43:53 ON 14 NOV 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'USPATFULL' ENTERED AT 20:43:53 ON 14 NOV 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
=> s beclomethasone or 4419-39-0/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
          9446 BECLOMETHASONE OR 4419-39-0/RN
=> s tiotropium or 136310-93-5/rn or 186691-13-4/rn or 411207-31-3/rn or
412010-60-7/rn or 412010-61-8/rn
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
           337 TIOTROPIUM OR 136310-93-5/RN OR 186691-13-4/RN OR
L5
411207-31-3/RN
                OR 412010-60-7/RN OR 412010-61-8/RN
=> s 14 and 15
L6
            44 L4 AND L5
=> s 16 and py<2000
   2 FILES SEARCHED...
1.7
             8 L6 AND PY<2000
=> dup rem 17
PROCESSING COMPLETED FOR L7
              8 DUP REM L7 (0 DUPLICATES REMOVED)
=> d 18 1-8
     ANSWER 1 OF 8 USPATFULL
L8
       2002:289804 USPATFULL
AN
TI
       Dispenser with doses' counter
IN
       Rand, Paul Kenneth, Redhill, UNITED KINGDOM
       Brand, Peter John, Royston, UNITED KINGDOM
       Godfrey, James William, Hertfordshire, UNITED KINGDOM
PA
       Smithkline Beecham Corporation, Philadelphia, PA, United States (U.S.
       corporation)
PI
       US 6474331
                          В1
                                20021105
       WO 9856446 19980608
                                                                      <--
       US 2000-445658
ΑI
                                20000331 (9)
       WO 1998-EP3379
                                19980608
                                20000331 PCT 371 date
PRAI
       GB 1997-11889
                           19970610
       GB 1997-21875
                           19971016
DT
       Utility
FS
       GRANTED
LN.CNT 633
```

INCLM: 128/200.230

INCL

```
INCLS: 128/203.120
NCL
       NCLM:
              128/200.230
       NCLS:
              128/203.120
IC
       [7]
       ICM: A61M016-00
EXF
       128/200.14; 128/200.23; 128/200.24; 128/200.25; 128/203.12; 128/203.15;
       128/203.19-203.25; 128/200.18; 116/280; 116/307; 116/308; 116/311-315;
       116/318; 116/319
L8
     ANSWER 2 OF 8 USPATFULL
       2002:262040 USPATFULL
ΑN
TI
       Medical aerosol formulations
       Keller, Manfred, Bad Krozingen, GERMANY, FEDERAL REPUBLIC OF
IN
       Herzog, Kurt, Basel, SWITZERLAND
PA
       Jago Research AG, Muttenz, SWITZERLAND (non-U.S. corporation)
                               20021008
PΤ
       US 6461591
                          В1
       WO 9834595 19980813
                                                                      <--
       US 1999-355883
ΑI
                                19990804 (9)
       WO 1998-CH37
                                19980202
                               19990804 PCT 371 date
PRAI
       CH 1997-248
                           19970205
       Utility
DT
FS
       GRANTED
LN.CNT 932
INCL
       INCLM: 424/045.000
       INCLS: 514/177.000; 514/263.340; 514/374.000; 514/471.000; 514/490.000;
              514/506.000; 514/646.000; 514/693.000; 514/699.000; 514/721.000;
              514/728.000; 514/730.000; 514/731.000; 514/736.000; 514/738.000;
              514/772.000; 514/957.000; 514/958.000
NCL
              424/045.000
       NCLM:
       NCLS:
              514/177.000; 514/263.340; 514/374.000; 514/471.000; 514/490.000;
              514/506.000; 514/646.000; 514/693.000; 514/699.000; 514/721.000;
              514/728.000; 514/730.000; 514/731.000; 514/736.000; 514/738.000;
              514/772.000; 514/957.000; 514/958.000
IC
       [7]
       ICM: A61K009-12
       ICS: A61K031-00; A61K047-00
EXF
       424/45; 514/957; 514/958; 514/975; 514/177; 514/263.34; 514/374;
       514/471; 514/490; 514/506; 514/646; 514/643; 514/699; 514/721; 514/728;
       514/730; 514/731; 514/736; 514/738; 514/772
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
L8
     ANSWER 3 OF 8 USPATFULL
AN
       2002:200714 USPATFULL
TΙ
       Dispenser with doses' counter
       Rand, Paul Kenneth, Redhill, UNITED KINGDOM
IN
       Brand, Peter John, Royston, UNITED KINGDOM
       Godfrey, James William, Hertfordshire, UNITED KINGDOM
       Bonney, Stanley George, Hertfordshire, UNITED KINGDOM
       Smithkline Beecham Corporation, Philadelphia, PA, United States (U.S.
PΑ
       corporation)
       US 6431168
                                20020813
PI
                           В1
       WO 9856444
                  19981217
                                                                      <--
       US 2000-445673
                                20000313 (9)
AΙ
       WO 1998-EP3377
                                19980608
                                20000313
                                         PCT 371 date
PRAI
       GB 1997-11889
                           19970610
       GB 1997-21875
                            19971016
DT
       Utility
FS
       GRANTED
```

```
LN.CNT 747
INCL
       INCLM: 128/200.230
       INCLS: 128/203.120; 128/200.180; 128/200.140; 128/203.230
NCL
              128/200.230
       NCLS:
              128/200.140; 128/200.180; 128/203.120; 128/203.230
IC
       [7]
       ICM: A61M016-00
EXF
       128/203.12; 128/200.18; 128/200.23; 128/200.14; 128/203.15; 128/203.19;
       128/203.23; 222/38; 222/36; 222/162
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
     ANSWER 4 OF 8 USPATFULL
L8
       2002:62596 USPATFULL
AN
TΙ
       Dispenser with doses counter
       Rand, Paul Kenneth, Redhill, UNITED KINGDOM
IN
       Brand, Peter John, Royston, UNITED KINGDOM
       Godfrey, James William, Hertfordhire, UNITED KINGDOM
PA
       SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S.
       corporation)
PΙ
       US 6360739
                          В1
                                20020326
       WO 9856445 19981217
                                                                      <--
ΑI
       US 2000-445659
                                20000331 (9)
       WO 1998-EP3378
                                19980608
                                20000331
                                         PCT 371 date
PRAI
       GB 1997-11889
                            19970610
       GB 1997-21875
                            19971016
DT
       Utility
FS
       GRANTED
LN.CNT 642
INCL
       INCLM: 128/200.230
       INCLS: 128/203.120; 128/200.180; 128/200.140; 128/203.230
NCL
       NCLM:
              128/200.230
       NCLS:
              128/200.140; 128/200.180; 128/203.120; 128/203.230
IC
       [7]
       ICM: A61M016-00
EXF
       128/203.12; 128/200.18; 128/200.23; 128/200.14; 128/203.15; 128/203.19;
       128/203.23; 222/38; 222/36; 222/162
T8
     ANSWER 5 OF 8 USPATFULL
AN
       2001:42141 USPATFULL
TI
       Nitrosated and nitrosylated compounds, and compositions and their use
       for treating respiratory disorders
IN
       Garvey, David S., Dover, MA, United States
       Letts, L. Gordon, Dover, MA, United States
       Renfroe, H. Burt, Wellesley, MA, United States
       Richardson, Stewart K., Ashford, CT, United States
PA
       NitroMed, Inc., Bedford, MA, United States (U.S. corporation)
PΙ
       US 37116
                          E1
                                20010327
                                19981020 (Original)
       US 5824669
                                                                      <--
                                19981223 (9)
AΙ
       US 1998-219476
       US 1996-620882
                                19960322 (Original)
       Reissue
DT
FS
       Granted
LN.CNT 1916
INCL
       INCLM: 514/174.000
       INCLS: 514/178.000; 514/179.000; 540/063.000; 540/066.000; 552/565.000;
              552/566.000; 552/575.000
NCL
       NCLM:
              514/174.000
       NCLS:
              514/178.000; 514/179.000; 540/063.000; 540/066.000; 552/565.000;
              552/566.000; 552/575.000
```

```
IC
       [7]
       ICM: A61K031-58
       ICS: C07J005-00; C07J007-00; C07J031-00; C07J071-00
       514/174; 514/178; 514/179; 540/63; 540/66; 552/565; 552/566; 552/575
EXF
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
     ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
L8
     1998:548517 CAPLUS
ΑN
DN
     129:166237
TΙ
     Fluorocarbon propellants for medical aerosol formulations
ΙN
     Keller, Manfred; Herzog, Kurt
     Jago Pharma A.-G., Switz.
PΑ
     PCT Int. Appl., 47 pp.
SO
     CODEN: PIXXD2
DT
     Patent
LA
     German
FAN.CNT 1
     PATENT NO.
                       KIND DATE
                                             APPLICATION NO.
                                                               DATE
                             _____
     ______
                      ____
                                             _____
     WO 9834595
                      A1
PI
                             19980813
                                             WO 1998-CH37
                                                               19980202 <--
         W: AU, CA, JP, NO, NZ, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE
     AU 9856496
                             19980826
                                             AU 1998-56496
                                                               19980202 <--
                        Α1
     AU 718967
                        В2
                             20000504
     EP 1014943
                        Α1
                             20000705
                                             EP 1998-900837
                                                               19980202
     EP 1014943
                       В1
                             20020619
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
FI
     JP 2001511160
                        T2
                             20010807
                                             JP 1998-533479
                                                               19980202
     AT 219355
                        Ε
                             20020715
                                             AT 1998-900837
                                                               19980202
     ZA 9800937
                        Α
                             19980806
                                             ZA 1998-937
                                                               19980205 <--
     NO 9903773
                        Α
                             19991004
                                             NO 1999-3773
                                                               19990804 <--
     US 6461591
                       В1
                             20021008
                                             US 1999-355883
                                                               19990804
PRAI CH 1997-248
                        Α
                             19970205
     WO 1998-CH37
                       W
                             19980202
RE.CNT 5
              THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
rs
     ANSWER 7 OF 8 USPATFULL
AN
       1998:128257 USPATFULL
TΙ
       Nitrosated and nitrosylated compounds and compositions and their use
for
       treating respiratory disorders
       Garvey, David S., Dover, MA, United States
Letts, L. Gordon, Dover, MA, United States
Renfroe, H. Burt, Wellesley, MA, United States
ΙN
       Richardson, Stewart K., Ashford, CT, United States
       NitroMed, Inc., Bedford, MA, United States (U.S. corporation)
PA
PΙ
                               19981020
       US 5824669
ΑI
       US 1996-620882
                                19960322 (8)
DT
       Utility
FS
       Granted
LN.CNT 1812
INCL
       INCLM: 514/174.000
       INCLS: 514/178.000; 514/179.000; 540/063.000; 540/066.000; 552/572.000;
               552/573.000; 552/575.000; 552/565.000; 552/566.000
NCL
       NCLM:
              514/174.000
              514/178.000; 514/179.000; 540/063.000; 540/066.000; 552/565.000;
       NCLS:
              552/566.000; 552/572.000; 552/573.000; 552/575.000
```

```
IC
       [6]
       ICM: A61K031-58
       ICS: C07J071-00; C07J007-00; C07J005-00
EXF
       552/572; 552/573; 552/575; 552/565; 552/566; 540/63; 540/66; 514/174;
       514/178; 514/179
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
     ANSWER 8 OF 8 USPATFULL
L8
       1998:98932 USPATFULL ,
AN
ΤI
       DHA-pharmaceutical agent conjugates of taxanes
       Shashoua, Victor E., Brookline, MA, United States
ΤN
       Swindell, Charles S., Merion, PA, United States
       Webb, Nigel L., Bryn Mawr, PA, United States
       Bradley, Matthews O., Laytonsville, MD, United States
       Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)
PA
PΙ
       US 5795909
                               19980818
       US 1996-651312
ΑI
                               19960522 (8)
DT
       Utility
FS
       Granted
LN.CNT 2451
       INCLM: 514/449.000
TNCL
       INCLS: 514/549.000
NCL
       NCLM:
             514/449.000
       NCLS: 514/549.000
IC
       [6]
       ICM: A61K031-335
       ICS: A61K031-22
EXF
       514/449; 514/549
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
=> d 18 1-8 ab kwic
L8
     ANSWER 1 OF 8 USPATFULL
AB
       There is provided a dispenser suitable for dispensing medicament,
       particularly medicament for use in the treatment of respiratory
       disorders. The dispenser comprises a housing (1) having a support (5);
       container (2), locatable within said housing (1), having an outlet (3),
       wherein said container (2) dispenses through said outlet (3) in
response
       to movement of the container (2), relative to the housing (1); and an
       actuation indicator having an indexing mechanism (13, 43) actuatable by
       movement of the container (2) relative to the housing (1). A couple
       mechanism (13, 43) is provided which couples the indexing mechanism
(13,
       43) to the container (2) to compensate for any variation in
       pre-actuation positionings of the indexing mechanism and container.
PΙ
       US 6474331
                          В1
                               20021105
       WO 9856446 19980608
DETD
                antiallergics, e.g., cromoglycate, ketotifen or nedocromil;
       antiinfectives e.g., cephalosporins, penicillins, streptomycin,
       sulphonamides, tetracyclines and pentamidine; antihistamines, e.g.,
       methapyrilene; anti-inflammatories, e.g., beclomethasone
       dipropionate, fluticasone propionate, flunisolide, budesonide,
       rofleponide, mometasone furoate or triamcinolone acetonide;
       antitussives, e.g., noscapine; bronchodilators, e.g., albuterol,
       salmeterol, ephedrine, adrenaline, . . fenoterol, formoterol,
       isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine,
       pirbuterol, reproterol, rimiterol, terbutaline, isoetharine,
```

tulobuterol, or (-)-4-amino-3,5-dichloro-.alpha.-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]methyl]benzenemethanol; diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium, tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins. . .

DETD . . . or the sulphate salt) or saimeterol (e.g., as the xinafoate salt) in combination with an antiinflammatory steroid such as a **beclomethasone** ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate).

CLM What is claimed is:

12. The drug product of claim 1, wherein the medicament is a member selected from the group consisting of **beclomethasone**, fluticasone, albuterol, salmeterol, ipratropium,

(-)-4amino-3,5-dichloro-

.alpha.[[[6-[2(2-pyridinyl)ethoxy]hexyl]methyl]benzenemethanol and salts, esters or solvates thereof.

16. The drug product of claim 12, wherein the medicament is beclomethasone dipropionate.

L8 ANSWER 2 OF 8 USPATFULL

AB A pressure-liquefied propellant mixture for aerosols, comprising a fluorinated alkane, in particular 1,1,1,2-tetrafluoroethane and/or 1,1,1,2,3,3,3-heptafluoropropane, and carbon dioxide, makes possible an improvement of the wetting properties of pharmaceutically active compounds, with which the formulation problems existing with hydrofluoroalkanes in relation to suspension as well as solution aerosols can be overcome and thus improved medicinal aerosol formulations can be obtained. With the aid of carbon dioxide, it is

also
possible to specifically influence the pressure and thus the particle
size distribution and also by displacement of oxygen from the
hydrofluoroalkanes to improve the storage stability of
oxidation-sensitive active compounds.

<--

PI US 6461591 B1 20021008

WO 9834595 19980813

DETD corticoids such as **beclomethasone**, betamethasone, ciclomethasone, dexamethasone, triamcinolone, budesonide, butixocort, ciclesonide, fluticasone, flunisolide, icomethasone, mometasone, tixocortol, loteprednol etc.,

DETD Using the propellant system according to the invention, it is possible to produce, for example, a **beclomethasone** metered aerosol which in comparison to a CFC-containing commercial product (Becotide.RTM., Glaxo Pharmaceuticals, Great Britain) has a far better dosage. . . is approximately halved and that in the "sample induction"

port" (artificial oropharynx) is reduced from about 50% to 20%. The **beclomethasone** formulation according to the invention thus makes it possible to design the metered aerosol more advantageously in relation to several. . .

DETD a) 2.5 g of **beclomethasone** dipropionate are weighed into a pressure addition vessel and dissolved with stirring in 55 g of ethanol,

in which 0.25. .

DETD . . . impacter according to USP 23 using puff Nos. 11-30 and 178-197 (3 canisters each, manual actuation). In all cases, the beclomethasone dipropionate was determined by means of HPLC and UV measurement at 230 nm. The mass median aerodynamic diameter MMAD was.

```
b) In the same manner as in paragraph a), a solution aerosol
formulation
       of beclomethasone dipropionate was prepared in HFA 227,
       ethanol and oleic acid, but the pressure was adjusted to 4.5 bar
       (20.degree. C.). . .
       15.6 g of beclomethasone dipropionate are dissolved in 811 g
DETD
       of ethanol which contains 3 g of oleic acid. The clear solution is
      mixed.
CLM
       What is claimed is:
       . aerosol formulation according to claim 1, wherein the
      pharmaceutically active compound is a corticoid selected from the group
       consisting of beclomethasone, betamethasone, ciclomethasone,
       dexamethasone, triamcinolone, budesonide, butixocort, ciclesonide,
       fluticasone, flunisolide, icomethasone, mometasone, tixocortol,
       loteprednol, and pharmaceutically acceptable salts thereof.
          does inhaler according to claim 10, wherein the pharmaceutically
       active compound is a corticoid selected from the group consisting of
       beclomethasone, betamethasone, ciclomethasone, dexamethasone,
       triamcinolone, budesonide, butixocort, ciclesonide, fluticasone,
       flunisolide, icomethasone, mometasone, tixocortol, loteprednol, and
       pharmaceutically acceptable salts thereof.
                                50-28-2, Estradiol, biological studies
      50-02-2, Dexamethasone
IT
      50-56-6, Oxytocin, biological studies
                                              50-67-9, Serotonin, biological
                51-34-3, Scopolamine 51-43-4, Epinephrine
                                                               51-55-8,
      studies
      Atropine, biological studies 57-27-2, Morphine, biological studies
                           76-25-5, Triamcinolone acetonide
                                                                76-42-6,
      57-42-1, Pethidine
                                                                119-13-1,
                  76-99-3, Methadone 113-15-5, Ergotamine
      Oxycodone
      .delta.-Tocopherol 124-94-7, Triamcinolone 302-41-0, Piritramide
      359-83-1, Pentazocine 361-37-5, Methysergide
                                                        378-44-9, Betamethasone
      437-38-7, Fentanyl 456-59-7, Cyclandelate
                                                    469-62-5,
                           561-27-3, Heroin 586-06-1, Orciprenaline
      Dextropropoxyphene
      596-51-0, Glycopyrrolate 1679-76-1, Drofenine 3215-70-1,
                     3385-03-3, Flunisolide 3703-79-5, Bamethan
      Hexoprenaline
      4419-39-0, Beclomethasone 4647-20-5, Icomethasone
                                                            5534-09-8,
      Beclomethasone dipropionate 5633-20-5, Oxybutynin
                                                              7182-53-8,
                            7683-59-2, Isoprenaline 9002-62-4, Prolactin,
      N-Butylscopolamine
                            9002-64-6, Parathyrin 9002-71-5, Thyrotropin
      biological studies
                                 9002-79-3, Melanotropin
                                                          9004-10-8, Insulin,
      9002-72-6, Somatotropin
                            9005-49-6, Heparin, biological studies
      biological studies
                   9007-92-5, Glucagon, biological studies 10405-02-4,
      Calcitonin
                          10539-19-2, Moxaverine
                                                    11000-17-2, Vasopressin
      Trospium chloride
      11096-26-7, Erythropoietin 13010-47-4, Lomustine 13392-18-2,
                  13669-70-0, Nefopam 16110-51-3, Cromoglycic acid
      18559-94-9, Salbutamol
                                20594-83-6, Nalbuphine
                                                         22254-24-6,
Ipratropium
                23031-25-6, Terbutaline 27203-92-
bromide 37148-27-9, Clenbuterol
                                           27203-92-5, Tramadol
                                                                   30286-75-0,
      bromide
                                                     41570-61-0, Tulobuterol
      Oxitropium bromide
      43229-80-7, Formoterol fumarate 51333-22-3, Budesonide
                                                                  51931-66-9,
                                              54063-54-6, Reproterol
                52485-79-7, Buprenorphine
      61951-99-3, Tixocortol 69049-73-6, Nedocromil 73573-87-2
76596-57-1, Broxaterol 80474-14-2, Fluticasone propionate
                                                         73573-87-2, Formoterol
81732-65-2,
                   85637-73-6, Atriopeptin
                                              86022-88-0, Cyclomethasone
      Bambuterol
      89365-50-4, Salmeterol 90566-53-3, Fluticasone 103628-46-2,
      Sumatriptan 105102-22-5, Mometasone 111406-87-2, Zileuton 120815-74-9, Butixocort 126544-47-6, Ciclesonide 129260-79-3,
```

Loteprednol 136310-93-5, Tiotropium bromide 139264-17-8,

Zolmitriptan (fluorocarbon propellants for medical aerosol formulations) L8 ANSWER 3 OF 8 USPATFULL AΒ There is provided a dispenser suitable for dispensing medicament, particularly medicament for use in the treatment of respiratory disorders. The dispenser comprises a housing (1) having a support (5); container (2), locatable within said housing (1), having an outlet member, wherein said container (2) is movable relative to the housing (1) to enable dispensing therefrom and said outlet member is connectable with said support (5) to prevent relative movement there-between; and a dose indicator (13, 43), locatable within said housing (1). The container (2) and dose indicator (13, 43) are reversably removable from the housing (1) as a single unit. PΙ US 6431168 В1 20020813 WO 9856444 19981217 DETD . antiallergics, e.g., cromoglycate, ketotifen or nedocromil; antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone dipropionate, fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone furoate or triamcinolone acetonide; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol, salmeterol, ephedrine, adrenaline, . . . formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, or (-)-4-amino-3,5-dichloro-.alpha.-[[[6-[2-(2-pyridinyl)ethoxy] hexyl]methyl]benzenemethanol; diuretics, e.g., amiloride; . anticholinergics, e.g., ipratropium, tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins. . . . or the sulphate salt) or salmeterol (e.g., as the xinafoate DETD salt) in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate). CLMWhat is claimed is: 22. The drug product of claim 17, wherein the medicament is selected from the group consisting of beclomethasone, fluticasone, flunisolide, budesonide, rofleponide, mometasone, triamcinolone, noscapine, albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, terbutaline, tiotropium, ipratropium, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, isoetharine, tulobuterol, (-) -4-amino-3,5-dichloro-.alpha.-{{ $6-{2-(2$ pyridinyl)ethoxy}hexyl}methyl}benzenemethanol, esters, solvates and salts thereof, and combinations thereof. 26. The drug product of claim 17, wherein the medicament is beclomethasone dipropionate. L8ANSWER 4 OF 8 USPATFULL AR There is provided a dispenser suitable for dispensing medicament,

particularly medicament for use in the treatment of respiratory

а

disorders. The dispenser comprises a housing (1) having a support (5),

container (2), locatable within said housing (1), having an outlet (3),

wherein said container (2) dispenses through said outlet (3) in response ${}^{\prime}$

to movement of the container (2) relative to the housing (1) and an actuation indicator having an indexing mechanism (13,43) actutable by movement of the container (2) relative to the housing (1). The indexing mechanism (13, 43) includes a coupling element to compensate for excess movement of the container (2) relative to the housing (1).

PI US 6360739 B1 20020326

WO 9856445 19981217

<--

DETD . . . antiallergics, e.g., cromoglycate, ketotifen or nedocromil; antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone dipropionate, fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone furoate or triamcinolone acetonide; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol, salmeterol, ephedrine, adrenaline, . . . isoprenaline,

metaproterenol,

phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, or (-)-4-amino-3,5-dichloro-alpha.-[[[6-[2-(2-pyridinyl)ethoxy] hexyl]methyl] benzenemethanol; diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium, tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins. . .

DETD . . . or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) in combination with an antiinflammatory steroid such as a **beclomethasone** ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate).

CLM What is claimed is:

12. The drug product of claim 11, wherein the medicament is selected from the group consisting of **beclomethasone**, fluticasone, flunisolide, budesonide, rofleponide, mometasone, triamcinolone, noscapine, albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, terbutaline, **tiotropium**, ipratropium, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, isoetharine, tulobuterol, (-)-4-amino-3,5-dichloro-.alpha.-{{{6-{2-(2-pyridinyl)ethoxy}hexyl}methyl} benzenemethanol, esters, solvates and salts thereof, and combinations thereof.

16. The drug product of claim 12, wherein the medicament is beclomethasone dipropionate.

L8 ANSWER 5 OF 8 USPATFULL

AB Disclosed are (i) compounds of a steroid, a .beta.-agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase (PDE) inhibitor directly or indirectly linked to a NO or NO.sub.2 group or a group which stimulates endogenous production of NO or EDRF in vivo;

at least one NO or NO.sub.2 moiety or a group which stimulates endogenous production of NO or EDRF in vivo, and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO.sup.+) or nitroxyl (NO.sup.-), or as the neutral species, nitric oxide (NO.circle-solid.) or that stimulates endogenous

```
production of NO or EDRF in vivo; and (iii) uses for them in preventing
       and/or treating respiratory disorders. ##STR1##
ΡI
       US 37116
                               20010327
                          E1
       US 5824669
                               19981020 (Original)
                                                                     <---
SUMM
       . . . pirbuterol, rimiterol, clenbuterol, bitolterol and repreterol,
       adrenalin, isoproterenol, ephedrine, orciprenlaine, fenoterol and
       isoetharine); anticholinergic agents (such as atropine, ipratropium,
       flutropium, tiotropium and rispenzepine) and mast cell
       stabilizers (chromolyn and nedocromil). Selective .beta. agonists have
       recently been developed with fewer cardiotonic side. . .
SUMM
       . . . asthmaticus. Nonetheless, the use of inhaled corticosteroids
       for the treatment of bronchial asthma has increased in recent years.
       Most frequently beclomethasone dipropionate, triamcinolone
       acetonide or flunisolide can be used to reduce or replace oral
       corticosteroid therapy, panicularly in the treatment of.
       corticosteroid therapy, panicularly in the treatment of. . .
. . contemplated .beta.-agonists include salmeterol, albuterol,
DETD
       metaproterenol, terbutaline, pitbuterol, rimiterol, clenbuterol,
       bitoterol and reproterol. Examples of contemplated anticholinergics
       include ipratropium, flutropium, tiotropium and rispenzepine.
       Examples of contemplated mast cell stabilizers include cromalyn and
       nedocromil. Examples of contemplated PDE inhibitors include filaminast,
       denbufyllene.
     ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
\Gamma8
AΒ
     A pressure-liquefied propellant mixt. for aerosols comprising a
     fluoridated alkane [esp. 1,1,1,2-tetrafluoroethane and/or
     1,1,1,2,3,3,3-heptafluoropropane (HFA 227)] and CO2 improves the wetting
     properties for pharmaceutical active substances, whereby existing
     formulation problems with hydrofluoroalkanes in suspension and soln.
     aerosols can be overcome and improved medical aerosol formulations can be
     obtained. By using CO2, the pressure and hence the particle size
     distribution can be influenced in a targeted manner, and by removing 02
     from the hydrofluoroalkanes the stability during storage of
     oxidn.-sensitive active substances can be improved. Thus, 1.5 kg HFA 227
     was gassed with CO2 and added at 6.5 bar and 20.degree. to a soln. of
     beclomethasone dipropionate 2.5 and oleic acid 0.25 in EtOH 55 q
     in a pressurized vessel; the mixt. was dispensed into Al aerosol
     canisters. The mean aerodynamic particle diam. and fine particle dose
per
     stroke of the dosing valve were .apprx.1.3 .mu.m and 61.5 .mu.g, resp.,
     immediately after filling the canisters; after 6 mo storage at 30.degree.
     and 70% relative humidity, these values were .apprx.1.3 .mu.m and 71.8
     .mu.g, resp.
PΙ
     WO 9834595 A1 19980813
     PATENT NO.
                      KIND DATE
                                           APPLICATION NO.
                                                             DATE
PΙ
     WO 9834595
                       A1
                            19980813
                                           WO 1998-CH37
                                                             19980202 <--
         W: AU, CA, JP, NO, NZ, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
SE
     AU 9856496
                       A1
                            19980826
                                           AU 1998-56496
                                                             19980202 <--
     AU 718967
                       B2
                            20000504
     EP 1014943
                       A1
                            20000705
                                            EP 1998-900837
                                                             19980202
     EP 1014943
                       В1
                            20020619
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
FI
     JP 2001511160
                       T2
                            20010807
                                            JP 1998-533479
                                                             19980202
                       E
     AT 219355
                            20020715
                                           AT 1998-900837
                                                             19980202
     ZA 9800937
                      Α
                            19980806
                                            ZA 1998-937
                                                             19980205 <--
```

NO 9903773

Α

19991004

NO 1999-3773

19990804 <--

```
US 6461591
                       В1
                            20021008
                                           US 1999-355883
                                                            19990804
AΒ
     . . Thus, 1.5 kg HFA 227 was gassed with CO2 and added at 6.5 bar
and
     20.degree. to a soln. of beclomethasone dipropionate 2.5 and
     oleic acid 0.25 in EtOH 55 g in a pressurized vessel; the mixt. was
     dispensed into Al. . .
     50-02-2, Dexamethasone 50-28-2, Estradiol, biological studies
IT
50-56-6,
     Oxytocin, biological studies
                                  50-67-9, Serotonin, biological studies
     51-34-3, Scopolamine 51-43-4, Epinephrine
                                                   51-55-8, Atropine,
     biological studies 57-27-2, Morphine, biological studies
                                                                  57 - 42 - 1,
                 76-25-5, Triamcinolone acetonide
                                                   76-42-6, Oxycodone
     Pethidine
     76-99-3, Methadone 113-15-5, Ergotamine
                                                119-13-1, .delta.-Tocopherol
     124-94-7, Triamcinolone
                              302-41-0, Piritramide
                                                       359-83-1, Pentazocine
     361-37-5, Methysergide
                              378-44-9, Betamethasone
                                                      437-38-7, Fentanyl
     456-59-7, Cyclandelate
                             469-62-5, Dextropropoxyphene
                                                             561-27-3, Heroin
     586-06-1, Orciprenaline
                             596-51-0, Glycopyrrolate 1679-76-1, Drofenine
                                                         3703-79-5, Bamethan
     3215-70-1, Hexoprenaline 3385-03-3, Flunisolide
     4419-39-0, Beclomethasone
                               4647-20-5, Icomethasone
     5534-09-8, Beclomethasone dipropionate
                                            5633-20-5, Oxybutynin
                                     7683-59-2, Isoprenaline
     7182-53-8, N-Butylscopolamine
                                                               9002-62-4,
     Prolactin, biological studies
                                     9002-64-6, Parathyrin
                                                             9002-71-5,
                   9002-72-6, Somatotropin 9002-79-3, Melanotropin
     Thyrotropin
     9004-10-8, Insulin, biological studies
                                            9005-49-6, Heparin, biological
              9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies
     10405-02-4, Trospium chloride 10539-19-2, Moxaverine
                                                              11000-17-2,
     Vasopressin 11096-26-7, Erythropoietin 13010-47-4, Lomustine
     13392-18-2, Fenoterol 13669-70-0, Nefopam 16110-51-3, Cromoglycic
acid
     18559-94-9, Salbutamol
                              20594-83-6, Nalbuphine
                                                       22254-24-6, Ipratropium
               23031-25-6, Terbutaline 27203-92-5, Tramadol
     bromide
                                                                30286-75-0,
     Oxitropium bromide 37148-27-9, Clenbuterol
                                                   41570-61-0, Tulobuterol
     43229-80-7, Formoterol fumarate 51333-22-3, Budesonide
                                                                51931-66-9,
                                            54063-54-6, Reproterol
              52485-79-7, Buprenorphine
     Tilidine
                              69049-73-6, Nedocromil
     61951-99-3, Tixocortol
                                                       73573-87-2, Formoterol
     76596-57-1, Broxaterol
                              80474-14-2, Fluticasone propionate
                                                                   81732-65-2,
     Bambuterol 85637-73-6, Atriopeptin 86022-88-0, Cyclomethasone 89365-50-4, Salmeterol 90566-53-3, Fluticasone 103628-46-2,
     Sumatriptan 105102-22-5, Mometasone 111406-87-2, Zileuton
     120815-74-9, Butixocort
                              126544-47-6, Ciclesonide 129260-79-3,
     Loteprednol 136310-93-5, Tiotropium bromide
     139264-17-8, Zolmitriptan
     RL: BAC (Biological activity or effector, except adverse); BSU
(Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study);
USES
     (Uses)
        (fluorocarbon propellants for medical aerosol formulations)
rac{1}{8}
     ANSWER 7 OF 8 USPATFULL
       Disclosed are (i) compounds of a steroid, a .beta.-agonist, an
AΒ
       anticholinergic, a mast cell stabilizer and a phosphodiesterase (PDE)
       inhibitor directly or indirectly linked to a NO or NO.sub.2 group or a
       group which stimulates endogenous production of NO or EDRF in vivo;
(ii)
       compositions of steroids, .beta.-agonists, anticholinergics, mast cell
       stabilizers and PDE inhibitors, which can optionally be substituted
with
       at least one NO or NO.sub.2 moiety or a group which stimulates
```

endogenous production of NO or EDRF in vivo, and a compound that

donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO.sup.+) or nitroxyl (NO.sup.-), or as the neutral species, nitric oxide (NO.circle-solid.) or that stimulates endogenous production of NO or EDRF in vivo; and (iii) uses for them in preventing and/or treating respiratory disorders.

PI US 5824669

19981020

<--

SUMM . . . pirbuterol, rimiterol, clenbuterol, bitolterol and repreterol, adrenalin, isoproterenol, ephedrine, orciprenlaine, fenoterol and isoetharine); anticholinergic agents (such as atropine, ipratropium, flutropium, tiotropium and rispenzepine) and mast cell stabilizers (chromolyn and nedocromil). Selective .beta. agonists have recently been developed with fewer cardiotonic side. . .

SUMM . . . asthmaticus. Nonetheless, the use of inhaled corticosteroids for the treatment of bronchial asthma has increased in recent years. Most frequently **beclomethasone** dipropionate, triamcinolone acetonide or flunisolide can be used to reduce or replace oral corticosteroid therapy, panicularly in the treatment of . . .

DETD . . . contemplated .beta.-agonists include salmeterol, albuterol, metaproterenol, terbutaline, pitbuterol, rimiterol, clenbuterol, bitoterol and reproterol. Examples of contemplated anticholinergics include ipratropium, flutropium, tiotropium and rispenzepine.

Examples of contemplated mast cell stabilizers include cromalyn and nedocromil. Examples of contemplated PDE inhibitors include filaminast, denbufyllene. . .

L8 ANSWER 8 OF 8 USPATFULL

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

PI US 5795909 19980818

<--

DETD Glucocorticoid: Amcinonide; Beclomethasone Dipropionate;
Betamethasone; Betamethasone Acetate; Betamethasone Benzoate;
Betamethasone Dipropionate; Betamethasone Sodium Phosphate;
Betamethasone Valerate; Carbenoxolone Sodium; Clocortolone Acetate;
Clocortolone Pivalate; Cloprednol;. . .

DETD . . . thiocoraline; thiofedrine; thiomarinol; thioperamide; thyroid stimulating hormone; tiagabine; tianeptine; tiapafant; tibolone; ticlopidine; tienoxolol; tilisolol; tilnoprofen arbamel; tiludronic acid; tinzaparin sodium; tiotropium bromide; tipredane; tiqueside; tirandalydigin; tirapazamine; tirilazad; tirofiban; tiropramide; topsentin; torasemide; toremifene; tosufloxacin;

trandolapril; traxanox; tretinoin; tretinoin tocoferil; triacetyluridine; tricaprilin;. . .

=>